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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,544	SCHULMAN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-52,54-59 and 61* is/are rejected.

7)☒ Claim(s) *53 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed July 9, 2004 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 37-61 are pending.

Applicants' amendment filed July 9, 2004 is acknowledged. Applicants' response has been fully considered. Claims 1-13, 16, 17, 21-23, 30, 31, 34 and 36 have been cancelled, and new claims 37-61 have been added. Therefore, claims 37-61 are examined.

Objection Withdrawn

3. The previous objection of claims 16 and 23 is withdrawn in view of applicants' cancellation of the claim, and applicant's response at page 7 in the amendment filed July 9, 2004.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 13, 16, 17, 21-23, 30, 31, 34 and 36, under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed July 9, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 37-52, 54-59 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating diabetes or type II diabetes, or

treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistence, or improving the control of glucose homeostasis in a mammal by administering a specific LXR agonist, compound 1, (structure shown at page 30, paragraph [0105]), wherein the treatment decreases hyperglycemia or insulin resistance, does not reasonably provide enablement for a method of treating diabetes or type II diabetes, or treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistance, or improving the control of glucose homeostasis in a mammal by administering an LXR agonist, wherein the treatment decreases hyperglycemia or insulin resistance, but the LXR agonist is not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 37-52, 54-59 and 61 encompass a method of treating diabetes or type II diabetes, or treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistance, or improving the control of glucose homeostasis in a mammal by administering a therapeutically effective amount of an LXR agonist. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides methods for preventing, halting or slowing the progression of metabolic diseases such as atherosclerotic cardiovascular diseases and related conditions in mammals by administering an LXRβ selective agonist (paragraphs [0013]), or methods for decreasing hyperglycemia and insulin resistance, treating type II diabetes and reducing cardiovascular complication of type II diabetes by administering a therapeutically effective amount of an LXR agonist to a mammal (paragraphs [0002] and [0018]). There are no

indicia that the present application enables the full scope in view of a method of treating type II diabetes or related disorders by administering an LXR agonist. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the LXR agonists and their treating conditions for type II diabetes or related which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for the use of a specific pan-LXR agonist, compound 1 (a sulfonamide) in the treatment of type II diabetes in the mice model (pages 38-39, paragraphs [0121]-[0122], Fig. 15).

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Shan *et al.*, WO 01/03705) indicates an LXR agonist having general formula ($C(R^1)(CX^1X^2X^3)(CX^4X^5X^6)(Ar\text{-}Y\text{-}R^2)$) can be used to treat atherosclerotic cardiovascular diseases and related conditions; Cao et al. (J. Biol. Chem. 278, 1131-1136 (2003), a post filing reference, provided by applicants) teach treatment of diabetic rodents with an LXR

agonist, T0901317 (having the same structure as Compound 1) resulted in dramatic reduction of plasma glucose; and Stulnig et al. (Diabetes 51, 2426-2433 (2002), a post filing reference, provided by applicants) teach treatment of adipocytes from 3T3-L1 cells and mouse embryonic fibroblasts in vitro with synthetic or natural LXR agonists decreases mRNA expression of 11β-HSD-1 (11β-hydroxysteroid dehydrogenase type 1) by ~50%, which is paralleled by a significant decline in 11β-HSD-1 enzyme activity, and 11β-HSD-1 appears to be casually linked to the development of type 2 diabetes and the metabolic syndrome, and indicate LXR ligands could mediate beneficial metabolic effects in insulin resistance syndromes including type 2 diabetes by interfering with peripheral glucocorticoid activation. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of various LXR agonists, their treating conditions and effects in the treatment of type 2 diabetes and related disorders to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass treating diabetes, type II diabetes, or treating type II diabetes, reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistence, or improving the control of glucose homeostasis using an LXR agonist, however, the identities of various LXR agonists, their treating conditions such as dosage and their effects in the treatment of type II diabetes and related disorders are not described in the specification, the invention is unpredictable regarding the effective amount of the LXR agonist used in treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating diabetes or type II diabetes, or treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistence, or improving the control of glucose homeostasis in a mammal by administering a therapeutically effective amount of an LXR agonist. The specification indicates the treatment with a specific pan-LXR agonist, compound 1 reduces hyperglycemia (elevated blood glucose) in the diabetic mice (pages 38-39, paragraphs [0121]-[0122], Fig. 15). However, the specification fails to demonstrate the use of various LXR agonists in the treatment besides compound 1, nor indicates the treating conditions and the effects of various LXR agonists in the treatment of type II diabetes or related disorders. Moreover, there are no working examples indicating the claimed methods associated with various LXR agonists other than Compound 1. Furthermore, the specification does not provide any specific guidance on the treating conditions such as dosage for different LXR agonists which have different structures from Compound 1. Since the specification fails to provide sufficient teachings on the use of various LXR agonists, nor indicates their effects in the treatment, it is necessary to have additional guidance on identities of LXR agonists and to carry out further experimentation to assess their effects, the experimentation is undue because further research is required to determine the effective dose of a LXR agonist in the treatment.

(6). Nature of the Invention

The scope of the claims includes treating type II diabetes or related disorders using an LXR agonist, but the specification does not describe the use of various LXR agonists in the treatment. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with variants, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect using various LXR agonists. Thus, practice of the full scope of the presently claimed invention based upon the current claims requires the practice of undue experimentation.

In response, applicants indicate the currently pending claims are fully enabled by the present specification and the knowledge of the skilled practitioner; in the response filed October 16, 2003, 2003 (pages 9-10), LXR agonists of various structures are known, however, it is the use of the agonist activity, rather than any particular structure, which is claimed as the invention. Since it is the activity that supports the use of the agonists in relation to glucose metabolism, it is entirely proper (and permitted, see MPEP 2173.05(g)) to claim the agonists by function rather than structure; Stulnig et al. (Diabetes, 51:2426-2433, 2002, a post filing reference) describe the effects of multiple LXR agonists with distinct structures (e.g., a synthetic LXR agonist T0901317, and two naturally occurring agonists, 22(R)-hydroxycholesterol and 20(S)-hydroxycholesterol) as able to downregulate 11β-hydroxysteroid dehydrogenase type 1 (11β -HSD-1) expression. Stulnig et al. note that 11β -HSD-1 appears to be causally linked to the development of type 2 diabetes and the metabolic syndrome" (see abstract), and further suggest that LXR agonists may "have beneficial effects on the metabolic control in patients with type 2 diabetes" (see page 2431), and LXR agonists have "the potential to exert positive effects on insulin sensitivity." (see pages 2429-2430, bridging paragraph); the fact that two independent groups of researchers (Cao et al. and Stulnig et al.) come to the same conclusion regarding the

ability to use structurally different LXR agonists in relation to diabetes clearly shows that there would have been no undue experimentation at the time of the invention to use LXR agonists of any structure in the methods of the invention as claimed; As for the reliance on an alleged need to define dosages for the use of additional LXR agonists, Applicants respectfully point out that no more than routine or repetitive experimentation is needed to determine dosages for various agonists. This is supported by the dose dependent effects on plasma glucose levels shown by Cao et al. (J. Biol. Chem. 278 (2), 1131-1136 (2003), using T0901317 as LXR agonist). Figure 15 of the instant application demonstrates how routine it is to determine effective dosages for reducing plasma glucose levels, e.g., a given LXR agonist, such as 22(R)-hydroxycholesterol or 20(S)-hydroxycholesterol, at a give dosage can be administered and compared to a control to observe the effects on plasma glucose levels over time (see Figure 15). Therefore, a person skilled in the art can experiment with a variety of LXR agonists at a variety of dosage to identify suitable dosage without undue experimentation (pages 7-11 of the response).

The response has been fully considered, however, the argument is not found persuasive because of the following reasons:

The specification only discloses a specific LXR agonist (compound 1, T0901317, a sulfonamide) at a specific dosage (50 mg/kg) reduces hyperglycemia mouse model of type II diabetes (paragraphs [0121] and [0122]). While the claims encompass numerous LXR agonists, the specification does not describe a genus of variants of LXR agonists in the method of treating type II diabetes or related disorders. Although the related art have reported many LXR agonists and the method of monitoring glucose, the treating conditions such as the dosage for various LXR agonists in the claimed method are not desclosed in the specification or the art. Applicants

argue that no more than routine or repetitive experimentation is needed to determine dosages for various agonists, Examiner disagrees because it requires further research to identify suitable dosage, which is undue experimentation. Applicants provides an example that a given LXR agonist, such as 22(R)-hydroxycholesterol or 20(S)-hydroxycholesterol, at a give dosage can be administered and compared to a control to observe the effects on plasma glucose levels over time (see Fig. 15; page 10, last paragraph of the response), however, the determination of this given dose requires further experimentation since 22(R)-hydroxycholesterol is structurally different from compound 1, the effect of 22(R)-hydroxycholesterol cannot be predicted using the dose-response curve of of compound 1.

Regarding applicant's comment on that it is entirely proper and permitted to claim the agonists by function rather than structure, MPEP 2173.05(g) indicates it is permitted to use function limitation rather than structure limitation, however, whether the function limitation is supported by 35 U.S. C. 112, first paragrph has to be evaluated. In the instant case, the specification does not describe a genus of variants of LXR agonists in the method of treating type II diabetes or related disorders, thus the claimed method with a functional limitation is not supported by the specification under 35 U.S. C. 112, first paragrph.

Regarding the referencea by Stulnig et al. and Cao et al., both are post filing references. Although Stulnig et al. teach different LXR agonists with distinct structures downregulate 11β-HSD-1 expression, where 11β -HSD-1 appears to be causally linked to the development of type 2 diabetes and the metabolic syndrome, and further suggest that LXR agonists may have beneficial effects on the metabolic control in patients with type 2 diabetes, the reference does not teach the use of various LXR agonists under in vivo conditions in the treatment of type 2

diabetes. As indicated by applicants, the reference only provides a possble mechanism which links 11β -HSD-1 to the development of type 2 diabetes using LXR agonists; and Cao et al. teach the use of a specfic LXR agonist T0901317 (compound 1) to reduce plasma glucose. Since the specification does not provide sufficient teachings, to practice of the full scope of the presently claimed invention based upon the current claims requires the practice of undue experimentation.

6. Claims 37-52, 54-59 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 37-52, 54-59 and 61 are directed to a method of treating diabetes or type II diabetes, or treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistence, or improving the control of glucose homeostasis in a mammal by administering a therapeutically effective amount of an LXR agonist. While the specification indicates the present invention provides a method of decreasing hyperglycemia and insulin resistance, treating type II diabetes and reducing cardiovascular complication of type II diabetes by administering a therapeutically effective amount of an LXR agonist to a mammal (paragraphs [0002] and [0018]), the specification does not disclose a genus of variants for LXR agonists used in the treatment of diabetes or related disorders.

The specification discloses a specific pan-LXR agonist, compound 1 (a sulfonamide) is used in the treatment of type II diabetes in the mice model (pages 38-39, paragraphs 0121-0122, Fig. 15). However, the specification does not describe a genus of variants for LXR agonists used

in the treatment of diabetes or related disorders. A single species of pan-LXR agonist, compound 1 does not provide original descriptive support for a genus of variants for LXR agonists. The variants for LXR agonists do not meet the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Applicants have described a specific pan-LXR agonist, compound 1 (a sulfonamide) is used in the treatment of type II diabetes in the mice model, however, a genus of variants for LXR agonists used in the treatment of diabetes or related disorders have not been described nor disclosed.

The skilled artisan cannot envision all the contemplated compounds for variants of LXR agonists. The detailed structure of variants of LXR agonists must be taught, therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of preparation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF'S were found unpatentable due to lack of written description for the broad class.

The claims are drawn to a method of treating diabetes or type II diabetes, or treating type II diabetes and reducing cardiovascular complication of type II diabetes, decreasing hyperglycemia or insulin resistence, or improving the control of glucose homeostasis in a mammal by administering a therapeutically effective amount of an LXR agonist, however, the specification does not provide original descriptive support over the instantly claimed genus of variants for LXR agonists used in the treatment of diabetes or related disorders.

Therefore, only those embodiments described and disclosed meet the written description requirement and not the full breadth of the claim meets the written description provision of 35 USC 1 12, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 49-52, 56-59 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 49 and 56 are indefinite because of the use of the term "partial agonist". The term "partial agonist" renders the claim indefinite, it is unclear what the term means since the specification does not define the term, e.g., does it mean the agonist is an LXRβ agonist and also

an LXRα agonist?, or does it mean the agonist has agonist activity toward LXRβ but not toward LXRα.

9. Claims 50-52 and 57-59 are indefinite because of the use of the term "an active agent". The term cited renders the claim indefinite, it is unclear what the active agent is, and what the active agent is used for. Claims 52 and 59 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

10. Regarding claims 50-52 and 57-59, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claims 51, 52, 58 and 59 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

11. Claim 61 is indefinite because of the use of the term "a method improving the control of glucose homeostasis in a mammal ". The term cited renders the claim indefinite, it is unclear to what reference point the control of glucose homeostasis is improved.

Claim Objections

12. Claims 53 and 60 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. Claims 37-52, 54-59 and 61 are rejected, and claims 53 and 60 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CMK
September 28, 2004